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# A Case for Randomized, Double-Blinded, Sham-Controlled Class III Medical Device Trials

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## YALE LAW & POLICY REVIEW

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### A Case for Randomized, Double-Blinded, Sham-Controlled Class III Medical Device Trials

Megan S. Wright\*

Class III medical devices, which are high-risk devices such as pacemakers and cardiovascular stents, must demonstrate evidence of safety and effectiveness in clinical trials prior to approval by the Food and Drug Administration (FDA).<sup>1</sup> In these clinical trials, patients are often, but not always, randomized into study conditions: a treatment group that receives the medical device, and a control group that does not. Randomization controls for extraneous differences between patients, and investigators can then determine how likely it is that the differences between the treatment and control group are related to chance.<sup>2</sup>

While randomization is one element of a high-quality clinical trial, the other two components—blinding and placebo-control condition—are generally absent because of the nature of the intervention studied. That is, it may be difficult, impracticable, or possibly unethical to design a clinical trial in which both the subject and the investigator are blinded as to who has received the medical device, and in which a sham device is used as a control for the placebo effect, the presence and power of which have been well documented in behavioral science and medical research.<sup>3</sup>

Given the absence of blinding and placebo-controls, bias of an unknown size is present in studies of Class III devices. This is because investigators and patients may unintentionally change their behavior in response to knowledge about who is in the treatment and control conditions, which can affect study

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1. 21 C.F.R. § 860.7(c) (2012).
2. Peter Armitage, *The Role of Randomization in Clinical Trials*, 1 STAT. MED. 345, 346 (1982).
3. See, e.g., Donald D. Price, Damien G. Finniss & Fabrizio Benedetti, *A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought*, 59 ANN. REV. PSYCHOL. 565 (2008).

results. Without blinding and placebo-controls, it is impossible to separate how much of the effect demonstrated in the study is due to these subconscious changes and how much is due to the medical device. Evidence of device effectiveness is thus not as strong as patients, physicians, and regulators may desire.

Scientifically rigorous studies of the safety and effectiveness of Class III medical devices are necessary, however, given that such devices are “high-risk devices that are very important to health or sustaining life”<sup>4</sup> or “present a potential, unreasonable risk of illness or injury.”<sup>5</sup> In the best scientifically designed trials, in order to test for an effect of a medical device that is surgically implanted, patients are randomized into a condition in which a “sham” procedure is conducted to control for the placebo effect, and the patients and evaluators are blinded as to whether the patient received the “real” or the “sham” device. There are ethical concerns about such studies because, although they are scientifically superior to non-randomized, unblinded, or uncontrolled studies, the sham arm of the trial may impose greater than minimal risk on study subjects for no corresponding direct benefit.

Much of the scholarly discussion on “sham” surgeries occurred in the late 1990s through the mid-2000s in response to a study in which investigators transplanted fetal tissue into the brains of patients with Parkinson’s disease and used a sham surgery as a control to assess whether the intervention was effective.<sup>6</sup> The issue of sham-controlled studies is emerging in importance again, however, as the FDA has recently been encouraging more Class III medical devices to be tested for safety and effectiveness in randomized, double-blinded, placebo-controlled studies,<sup>7</sup> the study design preferred for pivotal trials of ex-

4. Jill Jin, *FDA Authorization of Medical Devices*, 311 J. AM. MED. ASS’N 435 (2014). See also 21 C.F.R. § 860.93 (2014).
5. *Premarket Approval (PMA)*, FOOD & DRUG ADMIN. (Aug. 19, 2014), <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm>.
6. See, e.g., Thomas B. Freeman, Dorothy E. Vawter, Paul E. Leaverton, James H. Godbold, Robert A. Hauser, Christopher G. Goetz & C. Warren Olanow, *Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson’s Disease*, 341 NEW ENG. J. MED. 988 (1999) (describing the Parkinson’s study); Ruth Macklin, *The Ethical Problems with Sham Surgery in Clinical Research*, 341 NEW ENG. J. MED. 992 (1999) (critiquing the ethics of the sham intervention in the Parkinson’s study).
7. FDA, DESIGN CONSIDERATIONS FOR PIVOTAL CLINICAL INVESTIGATIONS FOR MEDICAL DEVICES: GUIDANCE FOR INDUSTRY, CLINICAL INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS AND FOOD AND DRUG ADMINISTRATION STAFF 31-32 (2013), <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf>. See also Thomas M. Burton, *Do the FDA’s Regulations Governing Medical Devices Need to be Overhauled?*, WALL ST. J. (Mar. 23, 2015), <http://www.wsj.com/articles/do-the-fdas-regulations-of-medical-devices-need-to-be-overhauled-1427079649>; Scott Gottlieb, *The FDA Wants You for Sham Surgery*, WALL ST. J. (Feb. 18, 2014), <http://www.wsj.com/articles/SB10001424052702304680904579365414108916816>; ANN QUINLAN-SMITH & RITA

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perimental drugs.<sup>8</sup> To date, most Class III devices have been approved on the basis of non-randomized, unblinded, or non-placebo-controlled trials, which makes the effectiveness of the devices questionable.

In this paper, I evaluate the ethical implications of the FDA's move to encourage randomized, double-blinded, sham-controlled trials for Class III devices when such studies are possible. In Part I, I describe the placebo effect and how researchers control for it. In Part II, I describe the results of studies of medical procedures and devices that have used a sham control. In Part III, I describe the ethical concerns surrounding the use of sham surgeries to study medical devices. In Part IV, I argue for the use of randomized, double-blinded, sham-controlled device trials, and propose an ethical framework for these studies.

## I. FDA REQUIREMENTS FOR DEVICE APPROVAL AND PLACEBO CONTROLS

The FDA requires that "valid" scientific studies of Class III devices provide "reasonable assurance" that such devices are safe and effective prior to their approval.<sup>9</sup> In order to demonstrate effectiveness, devices must be compared to a "control."<sup>10</sup> One such control is a placebo control (or "sham" device), which is particularly helpful when it is known or suspected that the real device will have a placebo effect.<sup>11</sup>

A placebo effect occurs when there is an effect from participating in a study that is not due to the effectiveness of the intervention being examined.<sup>12</sup> Such effects have been documented for both objective and subjective endpoints.<sup>13</sup> This effect could be from the research subject's expectations of improvement<sup>14</sup>

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KRAUS, N. AM. SCI. ASSOCIATES, CURRENT TRENDS AT THE FDA: IMPLICATIONS FOR DATA REQUIREMENTS, [https://www.namsa.com/wp-content/uploads/2015/10/NAMSA\\_-\\_Current\\_Trends\\_at\\_FDA-Implications\\_for\\_Data\\_Requirements\\_Jan2013.pdf](https://www.namsa.com/wp-content/uploads/2015/10/NAMSA_-_Current_Trends_at_FDA-Implications_for_Data_Requirements_Jan2013.pdf).

8. The FDA does exercise some regulatory flexibility, however, which means that some drugs are approved without being subjected to such studies. This means the clinical evidence of safety and efficacy is not as strong as it could be for some drugs approved by the FDA. See JERRY AVORN, *POWERFUL MEDICINES* 71 (2005).
9. 21 C.F.R. § 860.7(c)(1)-(2) (2012).
10. 21 C.F.R. § 860.7(f)(1)(iv). See also FDA, *supra* note 7, at 29-32 (describing types of controls).
11. See FDA, *supra* note 7, at 35.
12. *Id.* at 31.
13. *Id.* at 31-32, 35-36.
14. *Id.* at 31. This is known as a therapeutic placebo effect. Alex John London & Joseph B. Kadane, *Placebos that Harm: Sham Surgery Controls in Clinical Trials*, 11 *STAT. METHODS IN MED. RES.* 413, 423 (2002).

or changed behavior due to study participation.<sup>15</sup> It could also be from the receipt of better clinical care, spontaneous recovery, or regression toward the mean.<sup>16</sup> Placebo effects can be substantial, especially for studies involving surgeries,<sup>17</sup> and long in duration.<sup>18</sup>

In order to control for the placebo effect, a “sham” device can be used.<sup>19</sup> This device is designed to be ineffective, and so any effect demonstrated from its use is known to be a placebo effect, the size of which can then be compared to the effect size from the device being tested. If the effect from the real device is larger than the effect from the sham device, this is strong evidence of the device’s effectiveness.<sup>20</sup> Using a sham device as a control, along with a randomized, double-blinded study design,<sup>21</sup> allows for an isolation of the effect due solely to the device being tested.

Because the placebo effect introduces bias into the study, recent FDA guidance recommends using a placebo control in studies of device effectiveness whenever possible in order to control for this effect<sup>22</sup>—that is, to equalize the placebo effect across conditions.<sup>23</sup> The FDA recognizes that not all devices should be studied in this way, however. The FDA discusses ethical concerns of sham device controls in multiple places in the guidance document, particularly when these studies involve denying therapy to a group of subjects.<sup>24</sup> The FDA also considers the possibility and practicality of randomized, double-blinded, sham-controlled trials, noting that the scientifically preferred study design will not be feasible for some devices.<sup>25</sup>

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15. FDA, *supra* note 7, at 31-32, 35.

16. *Id.* at 32; London & Kadane, *supra* note 14, at 422-23.

17. Remy L. Brim & Franklin G. Miller, *The Potential Benefit of the Placebo Effect in Sham-Controlled Trials: Implications for Risk-Benefit Assessments and Informed Consent*, 39 J. MED. ETHICS 703, 704 (2013).

18. FDA, *supra* note 7, at 31.

19. *Id.* at 31.

20. *Id.*

21. The FDA also recommends randomization of subjects into different arms of the study and the blinding of all parties to the study—patients, investigators, and evaluators—whenever possible to reduce bias. If one or more of the parties is not blinded, then expectations and behavior change, which introduces bias of unknown size into the study regardless of whether subjects were randomized or not. FDA, *supra* note 7, at 31-37.

22. *Id.* at 31-32, 35-36.

23. Brian R. Wolf & Joseph A. Buckwalter, *Randomized Surgical Trials and “Sham” Surgery: Relevance to Modern Orthopaedics and Minimally Invasive Surgery*, 26 IOWA ORTHOPAEDIC J. 107, 107 (2006).

24. See, e.g., FDA, *supra* note 7, at 35.

25. *Id.* at 35-36; see also Richard J. Rohrer, *Sham Surgery*, 14 AM. MED. ASS’N J. ETHICS 227, 228 (2012).

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Published FDA guidance strongly encourages researchers to contact the FDA for technical assistance when designing medical device study protocols in order to receive FDA feedback prior to finalizing study protocols and submitting them for formal FDA review.<sup>26</sup> It is through this consultation between researchers and the FDA that decisions are made about whether a sham-controlled study will appropriately answer questions about the safety and effectiveness of the particular device. While there are other controls the FDA may consider acceptable for device studies,<sup>27</sup> all suffer from methodological weaknesses such as lack of blinding<sup>28</sup> or differing sizes of placebo effects.<sup>29</sup> Thus, the FDA has been requiring studies to use randomized, double-blinded, sham-controlled trials more frequently.<sup>30</sup>

## II. FINDINGS FROM STUDIES USING SHAM SURGERIES OR DEVICES

Conducting randomized, double-blinded, placebo-controlled drug trials in order to determine a drug's effectiveness is common. However, it is more difficult to conduct such studies of medical devices.<sup>31</sup> Because of this difficulty, many devices have not been subjected to the most scientifically rigorous studies

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26. See, e.g., FDA, *supra* note 7, at 11, 17-18, 51.

27. *Id.* at 30-31.

28. *Id.* at 36.

29. *Id.* at 32; Theodore J. La Vaque & Thomas Rossiter, *The Ethical Use of Placebo Controls in Clinical Research: The Declaration of Helsinki*, 26 APPLIED PSYCHOPHYSIOLOGY & BIOFEEDBACK 23, 24 (2001). The placebo effect size is larger for surgeries than for drugs. Brim & Miller, *supra* note 17, at 704. However, some argue that using the standard treatment as an active control can adequately demonstrate the effectiveness of the experimental treatment. See La Vaque & Rossiter, *supra*, at 31; Sophie L. Niemansburg, Johannes J. M. van Delden, Wouter J. A. Dhert & Annelien L. Bredenoord, *Reconsidering the Ethics of Sham Interventions in an Era of Emerging Technologies*, 157 SURGERY 801, 804 (2015).

30. This is despite any objections from researchers, clinicians, or the public. See, e.g., Gottlieb, *supra* note 7; (questioning the utility and ethics of sham surgery involving a cardiovascular device); Niemansburg et al., *supra* note 29, at 805 (describing possible objections by researchers and public to sham surgeries); Quinlan-Smith & Kraus, *supra* note 7, at 2 (describing physicians who felt some clinical trial designs were unethical); Wolf & Buckwalter, *supra* note 23, at 109 (describing potential public aversion to sham surgeries). Such objections to sham surgeries may be overstated, however, as empirical research has demonstrated support for sham-controlled trials. Samuel A. Frank, Renee Wilson, Robert G. Holloway, Carol Zimmerman, Derick R. Peterson, Kark Kieburz & Scott Y.H. Kim, *Ethics of Sham Surgery: Perspective of Patients*, 23 MOVEMENT DISORDERS 63 (2008); Niemansburg et al., *supra* note 29, at 805.

31. See Freeman et al., *supra* note 6, at 988.

for effectiveness.<sup>32</sup> A device may demonstrate an effect, but it may largely or only be due to investigator bias or the placebo effect.<sup>33</sup>

The few studies that have examined surgical procedures or devices using a sham control have found no effect of the surgical procedure or device relative to the sham procedure or device.<sup>34</sup> For example, recent research has shown that, twelve months out, a common surgical intervention to treat meniscal tears associated with degenerative knee disease is no more effective than a sham surgery.<sup>35</sup> In this procedure, the surgeon removes “torn meniscal fragments and [trims] the meniscus back to a stable rim.”<sup>36</sup> It was impossible to know this treatment was ineffective without comparing it to a sham because those undergoing the surgery experienced a placebo effect, which made the surgical intervention appear to be effective.<sup>37</sup> Prior to this study, patients had been subjected to the risks of surgery for no benefit beyond the placebo effect; patients and health insurers had paid for an ineffective intervention;<sup>38</sup> and intellectual and financial resources may also have been diverted from identifying an effective treatment for degenerative knee disease given popular belief that this intervention was effective.

Even more recently, a Medtronic blood pressure device, the Symplicity Renal Denervation System, was found to have no benefit relative to a sham device, according to preliminary study results.<sup>39</sup> According to the manufacturer’s website, the device, a catheter and generator that is inserted into the renal arteries, “emits a radio frequency (RF) energy across multiple electrodes . . . to disrupt the nerves,” which is thought to provide the proper energy to control hyperten-

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32. *Id.* at 988; Daniel B. Kramer, Shuai Xu & Aaron S. Kesselheim, *Regulation of Medical Devices in the United States and European Union*, 366 NEW ENG. J. MED. 848, 852 (2012); Burton, *supra* note 7.

33. See Freeman et al., *supra* note 6, at 991 (describing how some medical interventions are not evaluated using the gold standard of randomized, double-blinded, placebo-controlled studies, and thus the effectiveness of such interventions is unproven).

34. Rohrer, *supra* note 25, at 229.

35. Raine Sihvonen, Mika Paavola, Antii Malmivaara, Ari Itälä, Antii Joukainen, Heikki Nurmi, Juha Kalske & Teppo L.N. Järvinen, *Arthroscopic Partial Meniscectomy versus Sham Surgery for a Degenerative Meniscal Tear*, 369 NEW ENG. J. MED. 2515 (2013).

36. *Id.* at 2516.

37. *Id.*

38. See also Burton, *supra* note 7.

39. Gottlieb, *supra* note 7; Joseph Walker, *Medtronic Blood Pressure Device Misses Goal in Study*, WALL ST. J. (Jan. 9, 2014), <http://www.wsj.com/articles/SB10001424052702303393804579310183280286354>.

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sion.<sup>40</sup> On the basis of other, non-sham-controlled studies, the Symplicity Renal Denervation System was considered a “miracle” in reducing high blood pressure in patients that did not respond to drug treatment.<sup>41</sup> The E.U. approved the device,<sup>42</sup> and it is in use in Europe,<sup>43</sup> but the FDA required a sham-controlled study design to demonstrate safety and effectiveness prior to approval in the U.S.<sup>44</sup> While the device manufacturer describes the procedure as “minimally invasive,”<sup>45</sup> this procedure and device exposed European patients to the risks and costs of surgery for nothing more than a placebo effect.

## III. ETHICAL CRITIQUES OF SHAM SURGERY AND DEVICE STUDIES

The medical, bioethical, and philosophical literatures abound with ethical critiques of studies that use sham surgeries to evaluate the effectiveness of medical procedures and devices.<sup>46</sup> For many commentators, despite the scientific benefits that come from randomized, double-blinded, sham-controlled trials, such studies are too unethical to conduct.<sup>47</sup>

One common critique is that clinician-investigators conducting sham-controlled trials knowingly expose patients to the risks of surgery with no pro-

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40. *Symplicity RDN System*, MEDTRONIC, <http://www.medtronicrdn.com/intl/healthcare-professionals/about-rdn/about-the-procedure/index.htm> (last visited June 25, 2015).
  41. Joseph Walker, *Medtronic Makes Surprise Turn on Blood-Pressure Device*, WALL ST. J. (Mar. 29, 2014), <http://www.wsj.com/articles/SB10001424052702304688104579468500895597252>.
  42. In 2012, the FDA published a report on dangerous and ineffective devices that were approved in the European Union on the basis of limited evidence of safety and without evidence of benefit to patients. Most of the devices described were unsafe rather than ineffective. FDA, UNSAFE AND INEFFECTIVE DEVICES APPROVED IN THE EU THAT WERE NOT APPROVED IN THE US (May 2012), [http://www.elsevierbi.com/~media/Supporting%20Documents/The%20Gray%20Sheet/38/20/FDA\\_EU\\_Devices\\_Report.pdf](http://www.elsevierbi.com/~media/Supporting%20Documents/The%20Gray%20Sheet/38/20/FDA_EU_Devices_Report.pdf). The U.S. arguably has a more robust regulatory system for medical device approval than the E.U., which makes it less likely that unsafe devices will make it to the market, although some still do. However, because many devices approved by the FDA were not tested in the most rigorous type of clinical trial, there are still questions about device effectiveness in the U.S.
  43. Gottlieb, *supra* note 7; Walker, *supra* note 39.
  44. Gottlieb, *supra* note 7.
  45. *Symplicity RDN System*, *supra* note 40.
  46. There are methodological critiques of such studies as well. For example, the results may not be generalizable because the skill level of surgeons varies. Additionally, such studies cannot control for the increasing skill level of the surgeon over the course of the study. Freeman et al., *supra* note 6, at 988.
  47. See, e.g., Macklin, *supra* note 6.

spect of direct benefit.<sup>48</sup> The risks to patients include risks associated with the surgery itself, the anesthesia used for the surgery, and any follow-up testing and drug treatment.<sup>49</sup> This is in addition to the risks of forgoing or delaying other possible treatment.<sup>50</sup> Furthermore, unlike in randomized, double-blinded, placebo-controlled drug trials, surgeons<sup>51</sup> are forced to actively deceive patients in cases in which sham surgery is conducted.<sup>52</sup>

Another common critique is that while society as a whole may benefit from sham-controlled medical device trials as scientific knowledge advances, this benefit accrues at the expense of the research participants who do not benefit and are, in fact, harmed, and thus this study design violates the Declaration of Helsinki.<sup>53</sup> Some commentators argue that scientific advancement should not be prioritized over the ethical treatment of human subjects.<sup>54</sup>

Finally, some claim that forcing devices to go through sham-controlled trials instead of non-inferiority studies in which the control is an effective treat-

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48. See, e.g., Freeman et al., *supra* note 6, at 988; Gottlieb, *supra* note 7; Macklin, *supra* note 6, at 993.
  49. See, e.g., Freeman et al., *supra* note 6, at 990; London & Kadane, *supra* note 14, at 417; Macklin, *supra* note 6, at 993; Wolf & Buckwalter, *supra* note 23, at 108; Franklin G. Miller, *Sham Surgery: An Ethical Analysis*, 10 SCI. ENG'G ETHICS 157, 160 (2004).
  50. See, e.g., Freeman et al., *supra* note 6, at 990; London & Kadane, *supra* note 14, at 417; Macklin, *supra* note 6, at 993. These risks may also be present in drug trials that use a placebo, although some scholars view this as less controversial than sham controls in device trials because often this is not considered a "harm." London & Kadane, *supra* note 14, at 425; Miller, *supra* note 49, at 158; Sheryl Gay Stolberg, *Ideas & Trends: Sham Surgery Returns as a Research Tool*, N.Y. TIMES (Apr. 25, 1999), <http://www.nytimes.com/1999/04/25/weekinreview/ideas-trends-sham-surgery-returns-as-a-research-tool.html>. Some, however, believe it is unethical to withhold the standard effective treatment in order to study a new treatment, regardless of whether it is a drug or device trial. See, e.g., La Vaque & Rossiter, *supra* note 29, at 25, 34; Macklin, *supra* note 6, at 993.
  51. These studies can still be double-blinded if the surgeon is not the investigator or independent evaluator.
  52. Macklin, *supra* note 6, at 995; Franklin G. Miller & Ted J. Kaptchuk, *Sham Procedures and the Ethics of Clinical Trials*, 97 J. ROYAL SOC'Y MED. 576 (2004).
  53. See La Vaque & Rossiter, *supra* note 29, at 25; Wolf & Buckwalter, *supra* note 23, at 108. The Declaration of Helsinki was first adopted by the World Medical Association in 1964, and provides ethical guidelines for conducting medical research on human subjects. WORLD MED. ASS'N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2013), <http://www.wma.net/en/30publications/10policies/b3/index.html>.
  54. La Vaque & Rossiter, *supra* note 29, at 25; London & Kadane, *supra* note 14, at 418-19, 421.

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ment or device<sup>55</sup> delays getting devices to the market, which may be to the detriment of patients if the device is proven to work.<sup>56</sup>

## IV. THE NEED FOR RANDOMIZED, DOUBLE-BLINDED, SHAM-CONTROLLED DEVICE TRIALS

Much of the discussion and debate about the ethics of studies involving sham surgeries focuses on the possible harm to subjects participating in the sham arm of the study. Counterbalancing these considerations, however, is the possible harm to persons using ineffective devices that they believe are effective because the FDA has approved them based on non-randomized, unblinded, or non-sham-controlled studies. If it is possible, practicable, and not too risky to conduct a scientific study to determine whether a device is effective beyond the placebo effect, and such a study is not conducted, it is unethical to market these possibly ineffective high-risk Class III devices.<sup>57</sup> The FDA should encourage device manufacturers to provide only truly effective Class III devices.

Randomized, double-blinded, sham-controlled trials should thus be conducted whenever possible, practicable, and in accord with the Common Rule guidelines on human subjects research in order to secure FDA approval for Class III medical devices.<sup>58</sup> Such study design is the scientifically superior means by which to demonstrate the effectiveness of a device, particularly when endpoints are patient-reported or subjective,<sup>59</sup> and it reduces investigator bias.<sup>60</sup> Furthermore, sham surgeries can now be less invasive and risky than in the

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55. 21 C.F.R. § 860.7(f)(1)(iv)(c) (2012); Gottlieb, *supra* note 7.

56. Gottlieb, *supra* note 7; Walker, *supra* note 39.

57. As Miller asked: “Can it be ethical *not* to use sham surgery to evaluate rigorously a surgical procedure before it is introduced into practice under the following conditions: when methodological reasons indicate that a sham surgery control is needed to demonstrate efficacy and the risks of the sham procedure are not excessive and justified by the value of the knowledge to be gained from the study?” Miller, *supra* note 49, at 165.

58. Admittedly, such studies may not always be possible. Kramer, Xu & Kesselheim, *supra* note 32, at 852-53; Rohrer, *supra* note 25, at 228. Post-market surveillance studies can help determine safety and effectiveness of high-risk, implantable devices. Kramer, Xu & Kesselheim, *supra* note 32, at 853. However, the FDA does not have enough resources to adequately surveil all devices on the market. INST. OF MED., MEDICAL DEVICES AND THE PUBLIC’S HEALTH: THE FDA 510(K) CLEARANCE PROCESS AT 35 YEARS 103, 128 (2011) (“The Government Accountability Office (formerly the General Accounting Office) reported in 1989 and again in 2009 that the FDA was unable to manage its postmarket-surveillance responsibilities because of resource constraints . . .”).

59. Miller, *supra* note 49, at 157.

60. Wolf & Buckwalter, *supra* note 23, at 110.

past,<sup>61</sup> making the risk-benefit ratio of the research easier to evaluate and less controversial.<sup>62</sup>

This Part will first respond to the ethical critiques summarized in Part III, and then outline procedural safeguards that can facilitate ethical randomized, double-blinded, sham-controlled Class III medical device trials.

A. *Response to Ethical Critiques of Sham Device Study Designs*

In response to arguments about potentially unjustified risks to participants in the sham arm of medical device studies, some critics contend that sham procedures may be justified in cases where there is clinical equipoise.<sup>63</sup> Equipoise exists when “one’s judgment is ‘equally balanced’ with regard to the issue of help or harm that may ensue from assigning a patient to either the placebo or treatment group.”<sup>64</sup> This equipoise may come after a study of a device shows that it is more effective than the standard treatment, but leaves clinicians uncertain as to whether the effect is due to the placebo effect.<sup>65</sup>

Furthermore, some of the concerns regarding sham surgeries are minimized when the surgeries are not extreme. Many commentators reacted strongly to the Parkinson’s disease fetal-tissue implantation clinical trials because of the type of sham surgery performed.<sup>66</sup> In the study, surgeons drilled holes into the skulls of patients in the control group not having fetal-tissue implanted into their brains in order to make patients think they were in the treatment group, thus controlling for the placebo effect.<sup>67</sup> Importantly, this study design demonstrated that this high-risk treatment was ineffective.<sup>68</sup> Risks differ depending upon the procedure, however, and many sham procedures may be quite benign, such as a small skin incision and the use of local rather than general anesthesia.<sup>69</sup>

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61. See, e.g., Rohrer, *supra* note 25; Stolberg, *supra* note 50.

62. Some argue that because the risk-benefit ratio of sham surgeries is too uncertain, such surgeries should not be performed. See, e.g., Macklin, *supra* note 6, at 993-94. Others suggest that minimally invasive sham procedures may be ethically permissible. See, e.g., Gottlieb, *supra* note 7.

63. La Vaque & Rossiter, *supra* note 29, at 29-30; London & Kadane, *supra* note 14, 419-422.

64. La Vaque & Rossiter, *supra* note 29, at 29.

65. *Id.* There are debates about how to determine whether equipoise exists, however. *Id.* at 29-30; London & Kadane, *supra* note 14, at 420-21.

66. See, e.g., Macklin, *supra* note 6, at 995.

67. Freeman et al., *supra* note 6, at 989-90.

68. See Joshua David Rosenberg, *Informed Consent and Sham Surgery as a Placebo in Fetal Cell Transplant Therapy Research for Parkinson’s Disease*, 20 *EINSTEIN J. BIO. MED.* 14, 14 (2003) (describing the results of the Parkinson’s studies).

69. See Miller, *supra* note 49, at 163-64; Wolf & Buckwalter, *supra* note 23, at 109.

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Moreover, many of the aforementioned ethical concerns about risks to participants can be eliminated if a distinction is made between clinical ethics and research ethics, or clinical care and clinical research.<sup>70</sup> Clinicians and research scientists have different obligations toward patients, and in the case of medical device trials, the appropriate ethical standard for clinician-investigators is whether they are acting as ethical researchers. As Miller and Kaptchuk note: “Professional integrity for investigators conducting sham-procedure trials is preserved only by recognition that they are operating primarily as scientists, not as clinicians.”<sup>71</sup> What may be considered unethical for a clinician who must act in their patient’s best interest may not be considered unethical for a researcher as long as the risks of study participation are not excessive and have been minimized, the study has scientific value that justifies the risks, and informed consent has been obtained. Many people, after all, participate in studies with greater than minimal risk where there is only societal rather than direct individual benefit.<sup>72</sup>

When considering the objection that sham-controlled studies benefit science and society at the expense of participants, one can look for guidance in The Belmont Report.<sup>73</sup> The Belmont Report is one of the primary influences on United States human subjects research regulations; the Federal Policy for the Protection of Human Subjects is known as the Common Rule, which has been codified by many federal agencies.<sup>74</sup> The Belmont Report discusses the balancing of the interests of the individual and society,<sup>75</sup> and this is reflected in the Common Rule.<sup>76</sup> Empirical evidence also suggests that the majority of patients and the vast majority of clinician-investigators think it is ethically permissible for Institutional Review Boards (IRBs) to approve sham surgery studies, even if patients may prefer to participate in an unblinded trial.<sup>77</sup>

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70. Miller, *supra* note 49, at 158-59; Miller & Kaptchuk, *supra* note 52, at 577.

71. *Id.*

72. See Miller, *supra* note 49, at 164.

73. The Belmont Report was published in 1979 and describes ethical principles that should govern research on human subjects. NAT’L COMM’N FOR THE PROT. OF HUMAN SUBJECTS OF RESEARCH, THE BELMONT REPORT (Apr. 18, 1979), <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.

74. *Federal Policy for the Protection of Human Subjects* (‘Common Rule’), OFFICE FOR HUMAN RESEARCH PROTS., U.S. DEP’T. OF HEALTH & HUMAN SERVS., <http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html> [hereinafter *Common Rule*] (last visited Sept. 4, 2015).

75. *Id.* “Assessment of Risks and Benefits.” See also Wolf & Buckwalter, *supra* note 23, at 108.

76. *Common Rule*, *supra* note 74. The U.S. Department of Health and Human Services regulations can be found at 45 C.F.R. § 46 (2009).

77. Frank et al., *supra* note 30, at 68. Only half of Parkinson’s disease clinical researchers surveyed thought unblinded studies should be approved, and 94%

Finally, some contend that sham-controlled studies delay the entry of devices into the market, and that this delay harms patients.<sup>78</sup> However, devices that are approved quickly without being rigorously studied for effectiveness may ultimately be found to be ineffective<sup>79</sup> or even unsafe,<sup>80</sup> resulting in subsequent market withdrawal that may also be to the detriment of patients.

*B. Procedural Safeguards to Facilitate Ethical Randomized, Double-Blinded, Sham-Controlled Device Trials*

Given the ethical concerns described in Part III, there should be standard safeguards built into the study design, approval, and informed consent process for proposed sham-controlled studies. Each proposed sham-controlled study must still, however, be individually analyzed for its risks and benefits to ensure that the study design meets the Common Rule guidelines.<sup>81</sup>

The first set of safeguards relates to study design. Because of the increased risk to participants from sham surgery relative to using other possible controls or relative to the placebos used in drug trials, only rigorous study designs should be approved. This means that there should be a study design appropriately powered to answer the research questions,<sup>82</sup> blinding of all parties involved in the research,<sup>83</sup> and “accurate and complete data collection.”<sup>84</sup> Additionally, only investigators, surgeons, and evaluators with the necessary skill level should be involved in carrying out the study to ensure that the above requirements are met. Given the additional risks to subjects, it would be unethical

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approved of sham surgeries to study treatments for the disease. This study suggests a disconnect between investigators and potential research subjects in evaluating proposed research. *Id.* at 67. There may also be a disconnect between researchers and practitioners, the latter of whom may want to know how two treatments compare with one another, in which case blinding may not be possible, rather than how a treatment compares with nothing. La Vaque & Rossiter, *supra* note 29, at 31.

78. See, e.g., Gottlieb, *supra* note 7.

79. See, e.g., Kramer, Xu & Kesselheim, *supra* note 32, at 852; Walker, *supra* note 39; Gottlieb, *supra* note 7.

80. Burton, *supra* note 7.

81. See Miller, *supra* note 49, at 165.

82. Freeman et al., *supra* note 6, at 989.

83. *Id.* at 990; FDA, *supra* note 7, at 31-32, 35-36; Wolf & Buckwalter, *supra* note 23, at 110. Even when evaluators are blinded, patients often unblind them. Miller, *supra* note 49, at 162.

84. Freeman et al., *supra* note 6, at 989.

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to carry out a study of this nature without ensuring that the question of whether the device is safe and effective can be confidently answered.<sup>85</sup>

The second set of safeguards relates to study approval. All studies, regardless of design, must abide by the Common Rule regulations, which direct Institutional Review Boards to consider the risk-benefit profile of the study<sup>86</sup> and require that risks to subjects be minimized as much as possible.<sup>87</sup> This means that some sham device studies, although scientifically superior to other study designs, may not be approved if the risks to subjects are too extreme.<sup>88</sup> However, this may also mean that some studies that are approved expose subjects to greater than minimal risk.<sup>89</sup> Miller has asserted that the ceiling of risk for sham procedure controls “should be no greater than what would be permitted in nontherapeutic studies aimed at understanding pathophysiology.”<sup>90</sup> Brim and Miller have also argued that the benefit of the therapeutic placebo effect<sup>91</sup> should be factored into the risk-benefit analysis of these studies, especially given that the magnitude of the effect is larger for surgical interventions compared to drug trials; doing so will make it more likely that such studies will be approved.<sup>92</sup>

The FDA should also consider whether the device targets an important medical need in order to justify the risks associated with the sham device trial.<sup>93</sup>

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85. The studies should have both scientific and clinical value. *See* Freeman et al., *supra* note 6, at 988-89; Miller, *supra* note 49, at 163-64.
86. 45 C.F.R. § 46.111 (2009). Empirical evidence suggests that there is a disconnect between how researchers and subjects view research design. Frank et al., *supra* note 30, at 67. IRBs and government regulatory agencies should thus consult with patient advocates or patients for their viewpoint when reviewing studies that propose to use a sham device.
87. 45 C.F.R. § 46.111(a)(1). *See also* Freeman et al., *supra* note 6, at 988; Miller, *supra* note 49, at 163.
88. *See* Miller, *supra* note 49, at 163-64; Brim & Miller, *supra* note 17, at 704.
89. *See* Miller, *supra* note 49, at 164. This may be permissible if “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and [reasonable] to the importance of the knowledge that may reasonably be expected to result.” 45 C.F.R. § 46.111(a)(2).
90. Miller, *supra* note 49, at 164. That is, the ceiling is the risks permitted when healthy subjects volunteer for Phase I clinical trials.
91. Brim & Miller, *supra* note 17, at 703.
92. They argue this because the federal regulations say that all benefits need to be taken into consideration in the risk-benefit analysis, and all benefits need to be disclosed during the informed consent process. Brim & Miller, *supra* note 17, at 705. They assert that disclosing the placebo effect to prospective participants may actually increase enrollment in sham-controlled trials if participants know that they will receive some benefit from participating. *Id.*
93. Once more, the studies should have both scientific and clinical value. *See* Freeman et al., *supra* note 6, at 988-89; Miller, *supra* note 49, at 163-64.

It may be that there are already effective devices on the market, that alternative effective treatments are available, or that the condition is not serious enough to warrant a device targeted at it.<sup>94</sup>

The third set of safeguards involves informed consent, which is required as part of all research participation.<sup>95</sup> In the case of studies in which a sham device is used as a control, however, extra steps should be taken in the informed consent process.<sup>96</sup> One such step may be requiring prospective research participants to write, rather than just sign, a statement certifying that they understand they may be assigned to a condition in which they receive a sham device through sham surgery,<sup>97</sup> that they understand the risks of surgery,<sup>98</sup> and that the only such benefit of the study may be a placebo effect.<sup>99</sup> Another step may be to have a neutral third party, rather than the clinical investigator, go through the informed consent process and explain the difference between research and medical treatment in an effort to reduce any therapeutic misconception a prospective subject may have.<sup>100</sup> These informed consent safeguards mitigate concerns about clinician-researcher deception described above and promote patient autonomy. Concerns about the possible inequitable accrual of research benefits may also be lessened, given that prospective participants would knowingly and willingly decide to enter a study in which the benefits of the research may largely accrue to society rather than study participants, an option that some research suggests many patients would willingly choose.<sup>101</sup>

As a final ethical consideration, participants in the sham arm of the trial should be provided the device for free if it is found to be effective at the conclu-

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94. “[T]he FDA may consider the severity of the disease and available alternatives when evaluating high-risk devices” and may decline to approve such devices if there are safe and efficacious alternatives and if the device targets “quality of life rather than survival.” Kramer, Xu & Kesselheim, *supra* note 32, at 849-50. “[T]here must be a clinical need for the new device in the healthcare market.” Jin, *supra* note 4, at 435.

95. 45 C.F.R. §§ 46.111(a)(4), 46.116.

96. Freeman et al., *supra* note 6, at 989; Rosenberg, *supra* note 68, at 15-16 (addressing sham surgeries).

97. Miller, *supra* note 49, at 164-65.

98. See Rosenberg, *supra* note 68, at 17.

99. Brim & Miller, *supra* note 17, at 705. The language in the informed consent document may even be stronger: that participants will experience a placebo effect. This is because research has demonstrated large placebo effects in sham surgery studies. *Id.*; but see London & Kadane, *supra* note 14, at 424 (arguing that placebo effects should not be considered benefits and that they may actually be harmful).

100. See, e.g., Macklin, *supra* note 6, at 994 (describing the potential for therapeutic misconception); Rosenberg, *supra* note 68, at 17 (describing how to attack the therapeutic misconception); Wolf & Buckwalter, *supra* note 23, at 109 (describing the potential for therapeutic misconception).

101. Frank et al., *supra* note 30, at 67.

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sion of the study.<sup>102</sup> Another variation on this is to implant devices in all subjects, but only activate the devices in some (randomly and blindly).<sup>103</sup> This way, if the device is effective, a second procedure does not need to be conducted; even if the device is not effective, subjects will still benefit from the therapeutic placebo effect.<sup>104</sup> However, this variation would only work for a small subset of devices

## CONCLUSION

As the FDA is beginning to promote the use of randomized, double-blinded, sham-controlled Class III medical device trials,<sup>105</sup> in order to control for unconscious investigator bias from lack of blinding or the well-documented behavioral and physiological responses patients experience as a placebo effect,<sup>106</sup> it is necessary to determine whether this is an ethical policy. I have argued that with proper safeguards, along with an appropriate risk-benefit profile and informed consent, such studies can be ethical. Given the scientific superiority of such studies, the FDA should insist on this study design when it is possible, practicable, and ethical. This policy will ultimately benefit patients: although they may have delayed access to devices given the time it takes to conduct such studies, once a device is available, they will be assured access to a demonstratively effective device.<sup>107</sup>

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102. See Freeman et al., *supra* note 6, at 990; Sihvonen et al., *supra* note 35, at 2516; Gottlieb, *supra* note 7.

103. See, e.g., Rohrer, *supra* note 25 (summarizing this design for a device meant to combat obesity); Andres M. Lozano & Helen S. Mayberg, *Treating Depression at the Source*, SCI. AM., Feb. 2015, at 68-73 (describing a study of deep brain stimulation used to treat depression symptoms where all study subjects received implants, but the FDA required that a group of subjects not have their electrodes on for six months; there was no difference in relief of depression between the two groups). See also Gottlieb, *supra* note 7 (arguing that a sham component to a real surgery is ethically permissible).

104. See Brim & Miller, *supra* note 17, at 703.

105. FDA, *supra* note 7, at 31-32; Burton, *supra* note 7; Gottlieb, *supra* note 7.

106. Price, Finniss & Benedetti, *supra* note 3.

107. FDA, *supra* note 42, at 14-15; Kramer, Xu & Kesselheim, *supra* note 32, at 852; Walker, *supra* note 39.